A change in the trend in dosulepin usage following the introduction of a prescribing indicator but not after two national safety warnings

(Running title: Change in trend in dosulepin usage)

by

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Abstract

What is known and objective: The tricyclic antidepressant dosulepin has been associated with an increased risk of toxicity in overdose compared to other antidepressants. In the UK, the MHRA and NICE have issued advice on the prescribing of dosulepin, and a National Prescribing Indicator (NPI) to monitor usage was introduced in Wales in 2011. The aim of this study was to assess whether trends in dosulepin usage in Wales and NE England changed following the two pieces of safety guidance and the introduction of the National Prescribing Indicator in Wales.

Methods: Primary care dosulepin usage in the 12 months prior to and following MHRA safety advice (in 2007), NICE guideline CG90 (in 2009) and the introduction of the NPI (in 2011) was obtained. Usage was measured using Defined Daily Doses (DDDs) per 1,000 Prescribing Units (PUs). The trends in the 12 months prior to and following the introduction of prescribing advice and the NPI were compared using an autoregressive integrated moving average (ARIMA) model.

Results and discussion: In Wales, the trend in dosulepin usage did not change significantly prior to and following the MHRA advice: -0.18 and -0.43 DDDs/1,000PUs per month respectively ($p=0.07$), or prior to and following NICE CG90: -0.30 and -0.49 DDDs/1,000PUs per month respectively ($p=0.35$). In the 12 months prior to and following the introduction of the NPI the trend was -0.45 and -0.98 DDDs/1,000PUs per month respectively ($p=0.001$). In NE England the trend did not alter significantly following NICE advice or the introduction of the NPI in Wales.

What is new and conclusion: The trend in dosulepin usage in Wales altered significantly following the introduction of the NPI, but not after the other prescribing advice. This association, coupled with the absence of a significant change in NE England over the same period, provided some evidence of the effectiveness of the NPI in prompting a change in prescribing behaviour in Wales.

Introduction

Wales is a small nation (population 3.1 million in 2014) and shares a land border with England (population 54.3 million in 2014) with which it forms part of the United Kingdom (population 64.6 million in 2014).[1] Primary healthcare services in Wales are delivered by approximately 580 GP practices and 700 community pharmacies, and in England by approximately 8,000 practices and 11,000 pharmacies. Responsibility for the regulation of medicines and healthcare technologies in the United Kingdom lies with the Medicines and Healthcare Products Regulatory Agency (MHRA). Guidelines on clinical and cost-effective use of medicines and health technologies in England and Wales are provided by the National Institute of Health and Care Excellence (NICE). The All Wales Medicines Strategy Group (AWMSG) complements the work of NICE, particularly in relation to implementation in Wales of NICE guidelines (on specific therapeutic areas) and guidance (on single or multiple health technology appraisals). AWMSG works collaboratively with NICE through a memorandum of understanding first signed in 2012, and also with the MHRA on improving medicines safety through the Yellow Card Centre (Wales), part of the All Wales Therapeutics and Toxicology Centre.

The tricyclic antidepressant dosulepin has been found to have an increased risk of toxicity in overdose compared to other tricyclic antidepressants with the possible exception of doxepin.[2] In December 2007, an MHRA Drug Safety Update [3] made recommendations to minimise this risk, advising against initiation of dosulepin in new patients except under specialist supervision, and limiting the quantity of medication issued per prescription. Subsequently, in October 2009, the National Institute for Health and Care Excellence Clinical Guideline 90 (NICE CG90) “Depression: the treatment and management of depression in adults” strengthened previous MHRA advice stating “do not switch to, or start, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose”.[4]

The All Wales Medicines Strategy Group (AWMSG) has provided advice to Welsh Government on aspects of medicines management and safe and effective prescribing since its establishment in 2001. The use of national prescribing indicators (NPIs) to monitor primary care medicines usage in Wales in key therapeutic areas was introduced by AWMSG in 2004. Each NPI focuses on the prescribing of a specific medicine or group of medicines and is developed at a national multidisciplinary meeting of healthcare professionals. NPIs are evidence based and reviewed and updated annually to reflect changes in guidance and the publication of new evidence. The NPIs allow health boards, practices and prescribers to compare practice against an agreed standard. A target threshold is set based on the prescribing of the best performing 75th percentile of GP practices in Wales. GP practices are encouraged to move towards the NPI threshold and an improvement has been used as part of the Medicines Management component of the Quality and Outcomes Framework. The Quality and Outcomes Framework is a national incentive scheme operating across the whole of the UK, whereby practices receive financial reward for achieving targets.[5] In Wales, NPIs have also been used to encourage good prescribing as part of the Clinical Effectiveness Prescribing Programme (CEPP).[6] Performance has been monitored by health board prescribing advisors at a local level and by Welsh Government at a national level in order to compare prescribing between practices. An NPI encouraging a reduction in primary care dosulepin usage was introduced by AWMSG in April 2011, and retained for the financial years 2012–2013 and 2013–2014.[7]

Whilst randomised controlled trials (RCTs) represent the standard approach for assessing the outcome of many interventions, the methodology employed in these studies cannot be easily used to evaluate population level changes. The utility of natural experiments to overcome some of the limitations of RCTs in this regard has been recognised by the Medical Research Council.[8] In these studies data has typically been collected pre and post intervention, and the change over time analysed using interrupted time series analysis such as autoregressive integrated moving average (ARIMA) models.[9] Dosulepin prescribing in both Wales and

England may have been influenced by the MHRA and NICE CG90 advice. However, only usage in Wales has been subject to monitoring by a prescribing indicator. The publication of this prescribing advice and the regional differences between these potential influences on dosulepin usage formed the basis of a natural experiment to assess changes in GP prescribing behaviour in Wales and NE England.

The purpose of this study was to examine trends in dosulepin usage in Wales and NE England (an area with comparable demographic and socioeconomic characteristics to Wales [10]) prior to and following publication of the MHRA safety warning, NICE CG90 and the introduction of the AWMSG NPI. The rate of change in primary care dosulepin usage in the 12 months prior to and following the introduction of each intervention was analysed using an ARIMA model.

Methods

Data source

Monthly dosulepin usage data for Wales for the period from December 2006 to April 2012 was obtained using the Comparative Analysis System for Prescribing Audit (CASPA) version 1.0.4.7 (NHS Wales Shared Services Partnership [NWSSP]) accessed online March 2013. This software provides a record of all WP10 prescriptions (prescriptions issued by GPs in Wales for patients receiving NHS treatment) forwarded to Prescribing Services, NWSSP for processing and payment following dispensing. NE England was included as a comparator because of its similar demographic characteristics to Wales, and the absence of a prescribing indicator for dosulepin in England. This allowed an assessment of the impact of the AWMSG NPI in Wales in comparison with a control region where no prescribing indicator was used. Monthly primary care dispensing data for NE England for the period from July 2008 to April 2012 was obtained using ePACT.net (NHS Business Services Authority [NHSBSA]) accessed July 2013. The ePACT system provides details of FP10 prescriptions issued by GPs in England

and forwarded for processing and payment (i.e equivalent data to CASPA). However, in line with the NHSBSA data storage policy, information was only available for a period of 60 months from the time of access and there was no archive. Therefore, data for NE England for the period from December 2006 to June 2008 was unavailable when ePACT was accessed. Data obtained from both CASPA and ePACT used Daily Defined Doses (DDDs) per 1,000 Prescribing Units (PUs) as the prescribing measure. The defined daily dose (DDD) was developed by the World Health Organisation, as a unit of measurement whereby each medicine is assigned a value within its dose range. The value represents the assumed average daily maintenance dose of the medicine when used for its main indication in adults. The PU denominator controlled for changes in population, and provided weighting according to age (patients aged >65 years counted as three PUs, those <65 years one PU). The study was registered with Cardiff and Vale University Health Board Research and Development department (Ref: 14/CLC/5882) and ethical approval was not required.

Statistical analysis

For the purposes of analysis, dosulepin dispensing data obtained for Wales (December 2006 to March 2012) was subdivided into three distinct 24-month periods based upon the timing of the MHRA warning, NICE guideline CG90 and introduction of the AWMSG NPI. The trend (measured as rate of change in DDDs per 1,000PUs per month) in dosulepin usage during the 12 month periods prior to and following each piece of advice was compared using ARIMA analysis. Therefore, the rate of change from December 2006 to November 2007 (prior to MHRA guidance) was compared to that between December 2007 and November 2008. Similarly, the rate of change from October 2008 to September 2009 (prior to publication of NICE CG90) was compared to that seen between October 2009 and September 2010. Finally, the rate of change from April 2010 to March 2011 (prior to the introduction of the AWMSG NPI) was compared to that between April 2011 and March 2012. Due to the unavailability of dosulepin usage data for NE England until July 2008, analysis for this region was based upon the 12 month periods prior to and following the introduction of the NICE Guideline and AWMSG

indicator only. Significance was assumed at the $p<0.05$ level. Data were analysed using SPSS version 20 (IBM Corp, USA).

Results

Insert Figure 1 here

The prescribing of dosulepin in Wales and NE England during the period of study is shown in figure 1.

MHRA advice

Insert Figure 2 here

From December 2006 to November 2007, the rate of change of dosulepin usage was -0.18 DDDs/1,000 PUs per month in Wales. Following MHRA advice, from December 2007 until November 2008, the rate of change was -0.43 DDDs/1,000 PUs per month. The rates of change were not significantly different ($p=0.07$).

NICE guideline

Insert Figure 3 here

In the 12 months prior to the publication of NICE guideline CG90 (October 2008 to September 2009) the rate of change in dosulepin use in Wales was -0.30 DDDs/1,000 PUs per month. During the 12 month period from October 2009 to September 2010, the rate of change was -0.49 DDDs/1,000 PUs per month. The rates of change were not significantly different ($p=0.35$). In NE England, the rate of change in dosulepin use was -0.37 DDDs/1,000 PUs per month prior to publication of the NICE guideline, and -0.34 DDDs/1,000 PUs per month in the 12 months after September 2009. These rates of change were not significantly different ($p=0.87$).

AWMSG NPI

Insert Figure 4 here

From April 2010 to March 2011, (the 12 months prior to the introduction of the AWMSG NPI) the rate of change of dosulepin usage in Wales was -0.45 DDDs/1,000 PUs per month. From April 2011 until December 2012, the rate of change was -0.98 DDDs/1,000 PUs per month. These rates of change were significantly different (p=0.001). In NE England, the rate of change of dosulepin usage was -0.26 DDDs/1,000 PUs per month from April 2010 to March 2011, and -0.29 DDDs/1,000 PUs per month after April 2011. These rates of change were not significantly different (p=0.85).

Discussion

There were no statistically significant differences between the rates of change in dosulepin usage in Wales in the 12 months prior to and following publication of either the MHRA or NICE safety advice. The rate of change in dosulepin usage in Wales only altered significantly in the 12 months following the introduction of the AWMSG NPI in April 2011. Due to the non-availability of prescribing data for NE England between December 2006 and July 2008 changes in dosulepin usage in this region following the MHRA advice could not be assessed. However, the rate of change in dosulepin usage did not alter significantly following publication of NICE CG90, or during the 12 month period prior to and following April 2011 coinciding with the introduction of the NPI in Wales. The trends in dosulepin usage observed in this study suggested that there was a change in prescribing behaviour in Wales following the introduction of the AWMSG NPI.

The temporal relationship between the changes in dosulepin prescribing trend and introduction of the NPI provided some evidence that the indicator had an effect on GP behaviour. However, the retrospective, observational design of this natural experiment was a limitation, and did not allow a clear causal relationship between the introduction of the NPI and changes in drug usage to be established. In particular, other factors such as views of other opinion leaders[11] and pharmaceutical representatives[12] which have been shown to have an impact on GP prescribing behaviour could not be measured. The influence of pharmaceutical representatives

may have been a consideration, as newer antidepressants such as escitalopram and agomelatine would have been actively promoted during the period of this study and switching to these agents may have contributed to a change in dosulepin usage. However, it could be anticipated that the effect of this confounder would have been similar in both geographical regions, yet a significant change in the trend of dosulepin usage was specific to Wales. It was conceivable that the observed reduction in dosulepin prescribing trend was part of a more general reduction in the use of tricyclic antidepressants, and not a specific effect of the NPI. However, ARIMA analysis of the Welsh prescribing trend of the other tricyclic antidepressants licensed in the UK (amitriptyline, clomipramine, imipramine, lofepramine, and trimipramine) found no significant change in the 12 months pre and post introduction of the AWMSG NPI. Therefore the change appeared to be specific to dosulepin adding further support to an influence of the NPI. The change in the trend of dosulepin use in Wales after April 2011 may have been the result of a cumulative effect of the MHRA warning, NICE CG90 and the NPI, rather than an effect of the NPI alone. The inclusion of a geographically distinct control region (NE England) attempted to address this limitation. The absence of a significant change in the rate of dosulepin usage in NE England after April 2011 supported our hypothesis that the difference observed in Wales was related to a specific intervention (the introduction of the NPI) rather than a gradual effect over time.

It must also be noted that the data obtained from CASPA and ePACT used in this study gave a measure of prescriptions dispensed and submitted for pricing and did not necessarily directly correlate with prescribing in primary care. Therefore, prescriptions issued to patients but not subsequently taken to a pharmacy for dispensing would not be identified. The potential significance of this confounder was likely to be limited, as the number of dosulepin items dispensed each month and recorded on CASPA was relatively high (12,038 in Wales in March 2011) and it would be anticipated that the number of any non-dispensed prescriptions was small. This may have been particularly true in Wales due to the absence of a prescription

charge. If patients had received a prescription from a GP, they would have been less likely not to have it dispensed for financial reasons than in England, where prescription charges apply.

The MHRA safety warning and NICE CG90 were available to GPs in Wales and NE England and both therefore had the potential to influence dosulepin usage in each of the two regions. The absence of a change in the rate of usage following the publication of prescribing advice was a concern in light of the risk of toxicity associated with this antidepressant in overdose.[2] Whilst NICE CG90 stated "do not prescribe dosulepin", it was possible that prescribers placed greater emphasis on this advice for newly initiated patients, rather than for patients already receiving dosulepin. This may have resulted in a gradual reduction in DDD usage due to mortality or occasional review of existing patients, but not a significant change in prescribing trend in the 12 months following introduction of the NICE guideline. The introduction of the AWMSG NPI with a target threshold may have prompted GPs in Wales to review existing patients (as well as avoiding dosulepin for new patients) in order to bring their prescribing in line with the indicator. Consideration of both new and existing patients may have resulted in the significant reduction in dosulepin usage trend observed in this study. Variable effects on medicines usage in response to safety warnings, clinical guidelines and study findings have previously been reported.[13-15] Changes in rosiglitazone and pioglitazone prescribing in the Netherlands appeared to be associated with the publication of safety warnings.[13] In the Republic of Ireland, a warning of increased cardiac risk associated with celecoxib resulted in a significant change in prescribing behaviour, whereas warnings for clopidogrel, co-amoxiclav and haloperidol had little or no effect.[14] A number of factors, including lack of awareness of, and agreement with guidelines have been cited as barriers to change in prescribing behaviour.[11,16] Pharmacist involvement has been suggested as a method to overcome some of the barriers to change[17] and may have provided a mechanism through which the aim of the NPI was translated into practice. Primary care pharmacists working with GP practices in a number of the health boards in Wales have conducted work to reduce dosulepin usage in

response to the NPI. Engagement and collaboration between policy makers, primary care pharmacists and practices may help to maximise changes in prescribing behaviour.

Conclusions

The trend in dosulepin usage in Wales altered significantly following the introduction of the AWMSG NPI. The relationship between the timing of this change and the introduction of the NPI coupled with the absence of a significant change in the rate of usage in NE England over the same period provided evidence that the NPI may have prompted a change in prescribing behaviour. Despite the gradual decline in dosulepin usage seen in both of the geographical areas over time, the aim of introducing the NPI was to improve patient safety. Linking the observed change in prescribing to changes in patient outcomes is the subject of further work.

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Conflicts of interest
PND has declared financial support for attending symposia and honoraria for speaking engagements from Janssen-Cilag Ltd. PAR has declared that a clinical pharmacology training post in his Cardiff University Department was part funded by Astra-Zeneca under the ABPI training scheme until 2012. No other authors have any interests to declare.

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Figure legends

Figure 1: Monthly dosulepin usage in Wales and NE England over time.

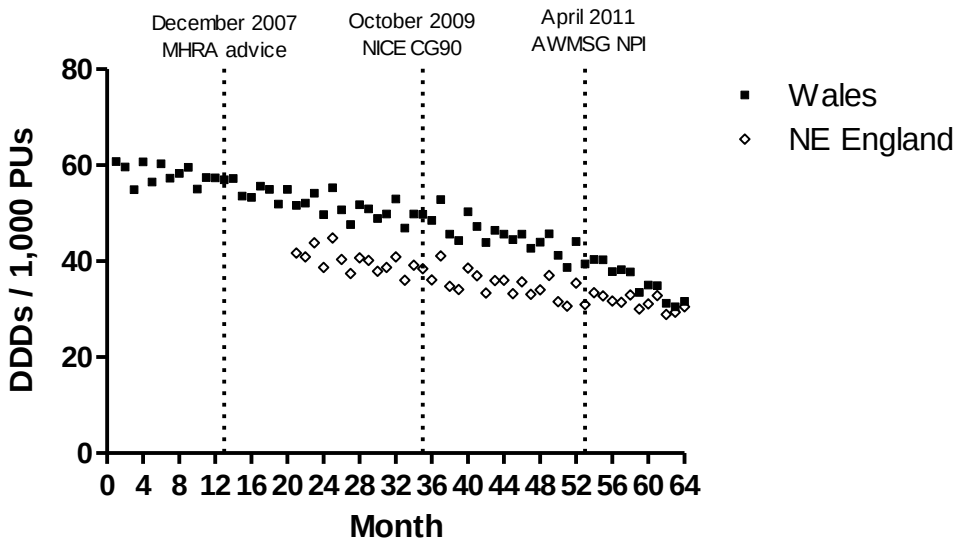

Figure 2: Monthly dosulepin usage in Wales in the 12 months prior to and following MHRA advice (issued December 2007).

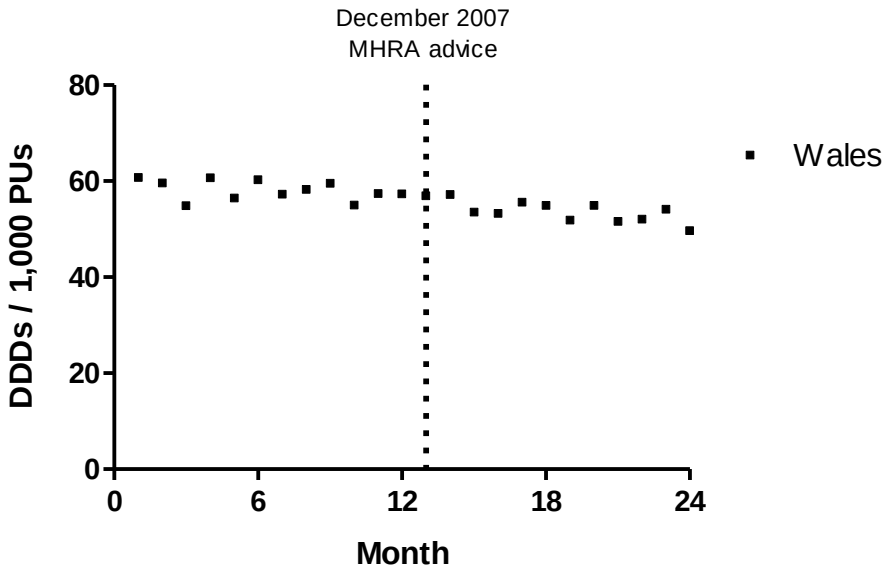

Figure 3: Monthly dosulepin usage in Wales and NE England in the 12 months prior to and following NICE CG90 (issued October 2009).

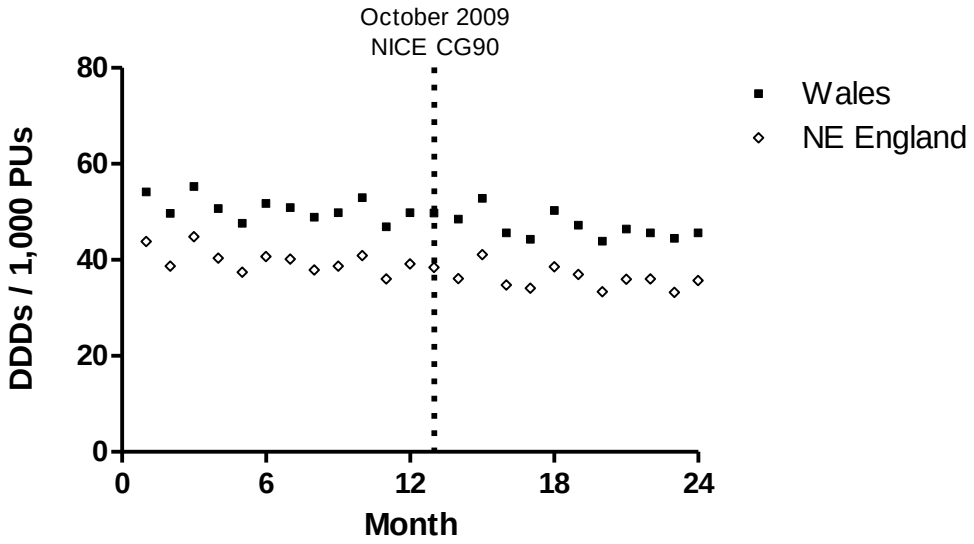

Figure 4: Monthly dosulepin usage in Wales and NE England in the 12 months prior to and following introduction of the AWMSG NPI (introduced April 2011).